IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 3998
MADGE *et al.*	Art Unit: 1614
Application No.: 10/658,971	Examiner: Brian Yong S. Kwon
Filed: September 9, 2003	Atty. Docket: 2451.0090008/BJD/GER
For: **Boronic Acid Salts Useful in Parenteral Formulations**	

Declaration Under 37 C.F.R. § 1.132 Of Dr. Anthony Kennedy

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Anthony James Kennedy, declare and state as follows:

1. I am the Vice President of Development at Trigen Limited. Trigen Limited is the assignee of this patent application. I am also a co-inventor of the subject matter claimed in this patent application.

2. I received a B.Sc. in Biochemistry from Surrey University, an M.Sc. in Neurochemistry from the Institute of Psychiatry, London University, and a Ph.D. in Biochemistry from the Institute of Ophthalmology, London University. I was also an MRC Post-Doctoral Research Fellow at the School of Pharmacy, London University. A copy of my *curriculum vitae* is attached.

3. I have reviewed and am familiar with the Office Action dated December 6, 2005, the Amendment and Reply filed January 6, 2006, the Supplemental Preliminary Amendment dated March 23, 2006, the Office Action dated March 30, 2006, the Office Action date July 25, 2006, the Amendment and Reply filed October 25, 2006, the final Office Action dated January 25, 2007, the Amendment and Reply filed April 19, 2007, and the Supplemental Amendment and Reply filed May 15, 2007. I have also reviewed and am familiar with the application as filed.

4. I have also reviewed and am familiar with the documents cited by the Examiner in the final Office Action: Claeson *et al.*, *Biochem J* 290:309-312, 1993 (hereinafter "Claeson"); Skordalakes *et al.*, *J. Am. Chem. Soc.*, 119: 9935-9936, 1997 (hereinafter "Skordalakes"); Kettner, WO 94/21668 (hereinafter "Kettner"); Wienand, WO 97/05161 (hereinafter "Wienand"); and Shoichet, WO 00/35904 (hereinafter "Shoichet").

5. I understand that the Examiner has rejected claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-120 as obvious over Claeson in view of Skordalakes, Kettner, Wienand and/or Shoichet. For the reasons I discuss in this Declaration, it is my opinion that one of ordinary skill in the art would not have expected, either at the priority date of the presently claimed invention or at its filing date, that the peptidyl boronic acid salts recited in the claims would be useful as therapeutic thrombin inhibitors. In order for a compound to be pharmaceutically useful as a parenteral thrombin inhibitor, it must have sufficient stability for an acceptable shelf life and the prior art relating to peptidyl boronic acids, especially Wu *et al.*, *J. Pharm. Sci. 89*: 758 (2000) (hereinafter "Wu", which I understand is of record in this application), gives the skilled person no reason to expect that base addition salts of such acids would provide improved stability over the unstable free acids, as I explain in the remainder of this Declaration.

6. As will be apparent from what I write below, there are a number of issues on which the examiner and I will find agreement:

- TRI 50b and similar peptidyl boronic acid thrombin inhibitors are in the prior art
- it was known how to convert such esters into the free acid
- it was known that the esters were prodrugs for the free acid.

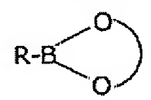
Yet by any standard the prior art relating to peptidyl boronic acids teaches away from formulating them as base addition salts and in favour of formulating them as esters for good reasons relating to stability. There are <u>many</u> documented instances of peptidyl boronic acids and their esters being isolated as **acid** addition salts but <u>none</u> that I know of their being isolated as **base** addition salts.

7. Before I discuss the teachings of Claeson, Skordalakes, Kettner, Wienand and Shoichet, which I believe the Examiner has particularly relied upon, I would like to put the present invention in context. The invention concerns peptidyl boronic acid thrombin inhibitors. However, the invention is not directed to novel peptidyl boronic acids but rather relates to the task of formulating a class of peptidyl boronic acids as parenteral pharmaceutical formulations. More particularly, the invention is directed to generic base addition salts of the described acids as active pharmaceutical ingredients (APIs) in parenteral drug formulations. As the Examiner has evidently appreciated, the Examples of the present application describe base addition salts of a representative peptidyl boronic acid designated TRI 50c.

8. When thinking about peptidyl boronic acids, it is always important to remember that they are not ordinary peptides, which have a carboxyl group in place of the boronyl group of a peptidyl boronic acid. After my 30 year career in drug development, largely based on traditional organic chemical pharmaceuticals, I was faced with unique difficulties when I started working on boron compounds, in that boron is quite different from carbon, does not behave like carbon and presents some unusual challenges in the pharmaceutical development arena. As is well known, boron has a vacant p orbital and is therefore an electrophilic electron acceptor and, unlike carboxylic acids, boronic acids can therefore coordinate with water to form $[RB(OH)_3]^-$ ions. The boron-oxygen bond is strengthened and shortened by ionic-covalent resonance and by $p\pi$-$p\pi$ bonding but a certain amount of $p\pi$-$p\pi$ bond energy is sacrificed when the vacant orbital accepts a pair of electrons to form a tetrahedral complex with approximately sp^3 hybridisation. The C-O bond energy has been reported as 560-790 kJ/mol and the B-O bond energy as 536 kJ/Mol. Note also that, since electronegativities increase across the periodic table, carbon is more electronegative than boron, and will tend to withdraw electrons from boron. (For authority on these issues, see F.A. Cotton and G. W. Wilkinson, *vide infra*).

9. The chemical differences between peptides and peptidyl boronic acids, therefore, are significant. No doubt the factors which I have mentioned in the preceding

paragraph contribute to one of these, which is the apparent inherent degradative instability of the boronyl group of peptidyl boronic acids in contrast to the stability of the peptidic carboxy group towards degradation. It is also noteworthy that peptidyl boronic acids are known not least from Gupta et al., International Patent Publication No. WO 02/059130 (hereinafter "Gupta", which I understand is of record in this application) to form with diols stable esters of the following structure:

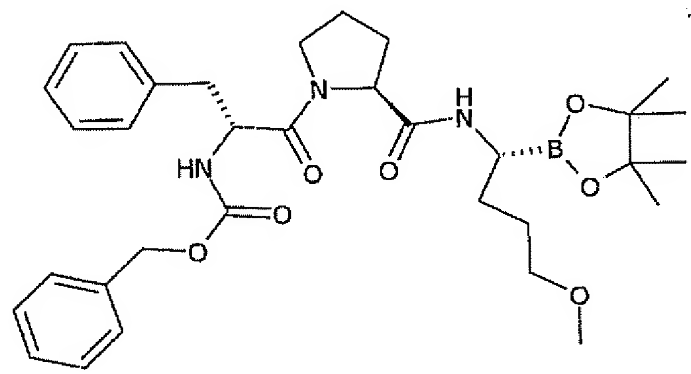


Carboxylic acids are evidently incapable of forming such a structure since the carboxyl group possesses only one –OH moiety. Gupta takes advantage of this stable diol structure to remedy the instability of one exemplified free acid, MG-341, which became known as bortezomib. It may be of interest that it is the unique chemistry of boron which enables peptidyl boronic acids to act as protease inhibitors: they enter the protease's active site and block it by forming a tetrahedral complex with surrounding amino acids called a "transition state analogue". Peptides alone do not do this effectively and it was found that, by replacing the C-terminal amino acid of a peptide having affinity for the thrombin active site with its boronic acid analogue, a tight-binding thrombin inhibitor is obtained (see for example Elgendy et al, *Tetrahedron Letters* 33: 4209 (1992), which I understand is of record in this application). This important difference between peptides and their boronic acid analogues illustrates the remarkable changes in chemistry which can be effected by replacing a carboxy group (-COOH) with a boronyl group ($-B(OH)_2$).

10. In view of the important chemical differences between boron and carbon, the skilled person would, to say the least, be extremely cautious in extrapolating from the physicochemical behaviour of a carboxylic acid drug to the physicochemical behaviour of a boronic acid drug. Equally, the special behaviour of boron limits the value of any teachings relating to acid addition salts of basic drugs when considering base addition salts of boronic acid drugs. In my view, therefore, the skilled scientist would not regard peptidyl boronic acids as conventional peptides as concerns their physicochemical

behaviour or formulation characteristics. Instead, he would look specifically at publications dealing with peptidyl boronic acids in these contexts.

11. The present invention relates to peptidyl boronic acid thrombin inhibitors and how to formulate them stably for parenteral pharmaceutical use. Within the class of compounds being claimed, a base addition salt of TRI 50c is being developed as a candidate active pharmaceutical ingredient (API). It is a second generation candidate API following on from a first generation candidate, which was a pinacol ester of TRI 50c known as TRI 50b:



(R,S,R)-TRI 50b Cbz-(R)-Phe-(S)-Pro-(R)-boroMpg-Pinacol

12. TRI 50b has never been commercialised as a drug. In fact free acid TRI 50c has never been sold as drug in any form, whether as the free acid or a derivative, e.g. a salt or ester. The Examiner has stated that TRI 50b is disclosed in Claeson, published as long ago as 1993: this is not entirely correct since Claeson discloses the <u>pinanediol</u> ester, which was designated TRI 50 (this code was not published, though). Some of TRI 50b's drug properties are described in "TRI 50b Non Confidential Information", Trigen Limited, July 2002, which I understand is of record in this application.

13. In any event, it is true that TRI 50b is in the prior art and I understand that, as well as Claeson, a good number of other prior art documents describing TRI 50b and other similar molecules have been submitted to the US PTO in connection with this

application, in the first Information Disclosure statement. Examples of these documents are mentioned on pages 9 and 10 of the application as filed under the heading "Neutral P1 Residue Boropeptide Thrombin Inhibitors".

14. To revert to Claeson, it indeed discloses boronic acid TRI 50c in the form of an ester of a diol, namely its pinanediol ester TRI 50. Although Claeson mentions that pinanediol ester TRI 50 hydrolyses spontaneously under physiological conditions (page 311, first sentence), TRI 50c was I believe always isolated in the prior art as an ester rather than as the free acid. As another example of synthesis and isolation of esters, see Deadman et al., *J. Med. Chem.* **1995**, *38*, 1511-1522 (hereinafter "Deadman"). Deadman was cited by the examiner of related application 10/659,178 and is I understand of record in this application, having been submitted in the first Information Disclosure Statement. Turning now to Deadman, it will be noted that all the compounds of the Deadman paper are disclosed by Deadman exclusively in the form of a diol ester, specifically the pinanediol or pinacol ester. Incidentally, there were prior examples of peptidyl boronic acids being made and isolated as esters (see for example Shenvi *et al.*, US Patent No 4,499,082, issued 12 February 1985, which I understand is of record in this application).

15. I agree with the Examiner that it was previously known that esters of boronic acids can be de-esterified. Indeed, it was well known before the present invention was made that the esters hydrolyse under physiological conditions and effectively act as prodrugs (see Claeson at page 311, first sentence, and Deadman at page 1512, right hand column, lines 19-22). For completeness, I would mention that Skordalakes shows the free acid of a sibling peptidyl boronic acid of TRI 50c. But, Skordalakes is concerned with crystallographic studies of the active principle (free acid) rather than with making a pharmaceutical formulation.

16. I agree with the Examiner that both Wienand and Shoichet mention salts, yet the end products of all their examples were free acids. I would like to mention at this point also that Shoichet relates to arylboronic acids, and that I would not compare their chemistry with that of peptidyl boronic acids, in view of the ability of boron to form $p\pi$-$p\pi$ bonds and the possibility of conjugation with the neighbouring π system of the

benzene ring. Kettner's examples meanwhile all describe acid addition salts. The Examiner of related application 10/659,178 also cited patent literature mentioning salts, namely De Nanteuil, U.S. Patent No. 5,814,622, (see column 3, lines 32-34)and Adams, U.S. Patent No. 5,780,454, (see Adams at column 9, lines 47-65). Yet, again, the only salts which de Nanteuil and Adams actually made were acid addition salts (many of de Nanteuil's examples describe hydrochloride or benzene sulfonate salts whilst Adams discloses a number of hydrochloride salts). Just as in the cases of Wienand and Kettner, no base addition salts are described as having been made in either de Nanteuil or Adams. Both de Nanteuil and Adams are I believe of record in the present application.

17. As I explain in more detail below, peptidyl boronic acids are unstable and TRI 50c has real stability problems which I consider to make the molecule itself extremely difficult or impossible to put into a parenteral pharmaceutical formulation with adequate stability (shelf life) for practical use. The invention, therefore, concerns the making of pharmaceutical formulations and, specifically, parenteral formulations. Neither Claeson, nor Skordalakes, nor Kettner, nor Wienand, nor yet Shoichet is concerned with making pharmaceutical formulations (nor are Adams or de Nanteuil), while the key technical advance achieved by the present invention relates precisely to pharmaceutical formulation. So I do not believe that any of these seven documents provides relevant insight into the central challenge addressed by the present invention.

18. This challenge was to identify derivatives of peptidyl boronates which would be stable enough for pharmaceutical use. My colleagues and I found that base addition salts of peptidyl boronic acid TRI 50c enhance the stability of the free acid. TRI 50c is a representative of the class of peptidyl boronic acids described in the application. I discuss the data (showing how stability is enhanced) in more detail below.

19. As I understand the Examiner's arguments, it is the Examiner's view that it would have been obvious to make base addition salts of any peptidyl boronic acid, for example the peptidyl boronic acids of Adams, since it was supposedly obvious to try base addition salts. To show that this is not the case, I would like to take the Examiner through the Adams' story. Adams relates among other things to peptidyl boronic acid

inhibitors of proteasome. A number of such compounds are listed in the Adams specification at column 15, lines 50 et seq., including at lines 54-55 N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid. The same molecule is disclosed as compound MG-341 in columns 59-60 of Adams. Pharmaceutically acceptable salts of the boronic acids are described as "preferred" at column 9, lines 47-50 of Adams, as too are esters of the acids at column 10, lines 11-12.

20. To the best of my knowledge, nobody before Adams had ever investigated whether a base addition salt of a peptidyl boronic acid would be a suitable form of the acid for formulation or administration, and I do not know how the authors of the patent specification concluded that such salts were preferred. I cannot believe that a skilled scientist would have taken this view. As I pointed out at the beginning of this Declaration, the chemical behaviour of boron is unique and there was in my opinion no basis whatsoever for supposing that base addition salts would be preferred, and I would think that the stated "preference" for salts, including base addition salts, came from the patent attorney's pen particularly as there are no examples of base addition salts in Adams. Events subsequent to the issue of Adams tend to confirm my opinion since later work (e.g. Gupta) shows that MG-341 was stably formulated as a mannitol ester and points away from base addition salts (Wu). (On the subject of salts, my recollection is that the literature contains ample examples of the actual preparation and isolation of acid addition salts of peptidyl boronic acids but, until the present invention, contained no such examples relating to a base addition salt of a peptidyl boronic acid. Some of the documents additional to Kettner, Adams and de Nanteuil which specifically mention acid addition salts of peptidyl boronic acids or their esters are Shenvi, WO 95/09858 (Fevig), WO 94/21650 (Amparo) and EP 0471651 (Metternich), all of which have I understand been made of record in the present application.).

21. After the publication of Adams, and ignoring other patent family members, the next publication relating to the chemistry of MG-341 took place in 2000 (Wu) so far as I know. Wu has the following to say at the foot page 758:

> *"The chemical stability of peptide boronic acid derivatives, from a formulation perspective, has not been extensively reported in the literature to our knowledge.*

During an effort to formulate 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ for parenteral administration, the compound showed erratic stability behaviour and was quite unstable in certain solvents."

Wu then describes various stability studies before stating the following in the final paragraph on page 763:

> *"Based on the known chemistry of boronic acids and the identity of the degradants, a degradation pathway of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ was proposed and is illustrated in Scheme 1. The initial oxidation can be attributed to peroxides or molecular oxygen and its radicals.* ***Because light, metal ions and alkaline conditions normally facilitate oxidation, these conditions should not be favorable to the stability of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ or any other alkyl boronic acid derivative.*** *Consistent with this conclusion is the observation that light accelerated the degradation of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$.* (Emphasis added).

22. In August 2002, more could be learned about the chemistry of 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ upon the publication of Gupta. Whilst Gupta relates to a class of boronic acids, all the examples describe 2-Pyz-(CO)-Phe-Leu-B(OH)$_2$ (i.e. MG-341) and it is plain that the application centres on that active principle. Gupta contains additional teaching relating to stability, commencing on page 2:

> *"Korcek et al., J. Chem. Soc. Perkin Trans 2 242 (1972), teaches that butylboronic acid is readily oxidised by air to generate 1-butanol and boric acid. These difficulties limit the pharmaceutical utility of boronic acid compounds......and limiting their shelf life.*
>
> *There is thus a need in the art for improved formulations for boronic acid compounds. Ideally, such formulations would be conveniently prepared, would exhibit enhanced stability and longer shelf life as compared to the free boronic acid compound......"*

23. Example 5 of Gupta describes the stability of a liquid formulation of MG-341 free acid. Despite containing ascorbic acid anti-oxidant, the liquid formulation was

not stable for longer than 6 months when stored at 2-8°C (page 26, paragraph [0148]). On the other hand, lyophilized D-mannitol ester of MG-341 was found stable over a period of 18 months ([0149]).

24. The final chapter in the Adams story is represented by the FDA-approved package insert for MG-341, now called bortezomib (Velcade®). A copy of the package insert (13 May 2003) is annexed hereto, and it will be seen that the drug is sold as a lyophilized powder of the mannitol ester of the free boronic acid.

25. It has long been known that boric acid ($B(OH)_3$) is a weak acid. See for example *Advanced Inorganic Chemistry, A Comprehensive Text*, F A Cotton and G W Wilkinson, Third Edition 1972, John Wiley and Sons Inc, which states on page 230 that "[Boric acid] is a very weak and exclusively monobasic acid that is believed to act, not as a proton donor, but as a Lewis acid, accepting OH^-". In my opinion, at the present invention's priority date (9th September 2002), the chemist of ordinary skill would therefore have concluded, as he still would now, that peptidyl boronic acids are weak acids. It is well known that the salts of weak acids with strong bases form basic solutions, as in the case of sodium acetate. A reasonable prediction would therefore have been that salts of peptidyl boronic acids with a strong base such a sodium hydroxide would form basic solutions so, following Wu, negatively affecting stability. Similarly, exposure of the acid to base would be feared to have a negative effect on stability.

26. I reiterate that the present invention relates to making parenteral pharmaceutical formulations of, in particular, a peptidyl boronic acid previously investigated in the form of an ester, namely pinacol ester TRI 50b. In my opinion, therefore, the man of ordinary skill seeking to formulate a peptidyl boronic acid in September 2002 would have looked at the available information on making pharmaceutical formulations of such compounds as mentioned in paragraphs 21-23 above, and from these documents and from what I believe would have constituted his common general knowledge (see paragraph 25 above), he would have gleaned the following information:

- peptidyl boronic acids are prone to oxidative degradation and, because light, metal ions and alkaline conditions normally facilitate oxidation, these conditions should not be favorable to stability
- peptidyl boronic acids are weak acids and will form alkaline solutions with strong bases
- base addition salts of peptidyl boronic acids had never been tested for their suitability for formulating
- but their esters had been so tested (e.g. Gupta, TRI 50b)
- bortezomib was excessively unstable (Gupta, also Wu)
- bortezomib was stabilized by manufacture as an ester, namely its lyophilized D-mannitol ester.

27. The facts relating to formulation of peptidyl boronic acids as I see them, therefore, point in September 2002 firmly in the direction of making esters for stability: base addition salts were unexplored. Insofar as any relevant guidance could be found in the literature describing peptidyl boronic acids, I believe that the sole pointer available was the teaching of Wu that alkaline conditions should be avoided. Anyone reading the teachings of Wu regarding the destabilizing effect of alkaline conditions, would be surprised to learn that a peptidyl boronic acid could be stabilized by combining the acid with alkali, to form a salt. These views would have been further confirmed in September 2003 by the publication in May 2003 of the bortezomib package insert.

28. The prejudice against exposing the compound to alkaline conditions is specific to boronic acid chemistry which, as I explained at the outset, is very different from the more mainstream carboxylic acid chemistry. The skilled person already knows from his own knowledge as well as from Wu that peptidyl boronic acids will not behave like ordinary peptides or other conventional pharmaceuticals. So far as I am aware, a boronic acid drug has never previously been changed from its free acid to a salt form to improve its characteristics for the purposes of formulation or administration.

29. Claeson (1993), Kettner (1994), Wienand (1997), Skordalakes (1997) and Shoichet (2000) are entirely silent as to the benefits or otherwise of base addition salts of peptidyl boronic acids; so too are de Nanteuil and Adams. Science advanced between 2000 and 2002 and we have the benefit of knowing what studies were conducted on the stability of boronic acids after 2000, what predictions these studies led to and what routes the skilled chemist actually took to formulate them. Thus, Wu suggests to me that base addition salts would be a bad idea and Gupta that lyophilized D-mannitol esters would be an excellent idea. As a matter of interest, Gupta's predictions turned out to be substantiated by the bortezomib package insert (13 May 2003).

30. The skilled reader of Claeson would in my opinion have had no reasonable expectation that base addition salts of the peptidyl boronic acids described in the claims of the present application would have enhanced stability. The reasons are that Wu teaches that alkaline conditions favour oxidation whilst formation of a salt from an acid requires addition of alkali. The mention of salts in Wienand, Shoichet, Adams and de Nanteuil is to my eyes so-called "boilerplate" written by a patent attorney in relation to patent applications framed to protect new peptidyl boronic acid protease inhibitors, and cannot be seriously regarded as scientific teaching on meeting the challenges of formulating such acids, especially since these four patent specifications mention no such challenges (e.g. the challenge of shelf life and its associated requirement for adequate stability). The skilled scientist working on drug formulation would not find in these four patent specifications any useful teaching as to how a scientist should address the challenges of formulating a pharmaceutical drug for parenteral (or other) administration and would look at these four patents/applications no further. Moreover, those who developed Adams' unstable molecule bortezomib decided to stabilize it by derivatisation as a mannitol ester. The skilled man would I believe have been motivated by this history to make and test a mannitol ester of a peptidyl boronic acid drug. In just the same way, serious scientific study of Wu would I believe have pointed the skilled person away from base addition salts for the reasons I have already described.

31 Against the teaching that peptidyl boronate salts would be unstable, the present invention counterintuitively achieves stability for the defined class of peptidyl

boronic acids by formulating them as boronate salts. The data demonstrating this finding are in my view compelling. In this regard, I refer to attached Appendix A. The first part of Appendix A is a Summary Stability Report for the free acid TRI 50c. Table 1 of the report shows that the free acid degraded dramatically over three months. Table 2 shows that, after three months at 25°C, the purity as measured by HPLC decreased from 97.18% to 58.83%. The second part of Appendix A is a Summary Stability Report for TRI 50c sodium salt, which shows that, after three months at 25°C, the purity as measured by HPLC decreased to 95.3%.

32 The data in the stability report are consistent with the stability data obtained in Example 34 of this application, in which sodium and lysine salts were shown to be more stable than the free acid. The data in the stability report are also consistent with the data reported in Example 28 of US Patent Application No 10/659,178, which shows the encapsulated lysine salt to be more stable than the free acid, and with Example 13 of U.S. Patent No. 7,112,572, which shows that calcium salt of TRI 50c is more stable than the free acid.

33. To summarise the stability data, the data mentioned in paragraphs 31 and 32 above relate to sodium, lysine and calcium salts of free acid TRI 50c and show that all three salts are more stable than the comparative free acid.

34. As I stated above, Wienand and Shoichet are not relevant to the present invention. If any further confirmation were needed of this, a comparison between the above data and the teaching of Wienand and Shoichet will serve. Thus Wienand expressly teaches on page 5, lines 17-18 that free acid (I) is useful as a pharmaceutical, whilst Shoichet describes that free acids (1) can be included in a pharmaceutical formulation (page 11, lines 14-17). Neither Wienand nor Shoichet (nor Claeson, nor Skordalakes, nor Kettner, nor Adams, nor de Nanteuil) gives any indication that peptidyl boronic acids are insufficiently stable for practical use and can be stabilized by being converted to base addition salts. In contrast, the data presented above show that:

- TRI 50c itself, the free peptidyl boronic acid, is apparently too unstable to be pharmaceutically useful
- derivatisation of TRI 50c as a range of base addition salts increases stability.

The above findings contradict the teachings of Wienand and Shoichet who both teach to the effect that their free acids are pharmaceutically useful and equate them with their salts. Wienand and Shoichet therefore cannot be relevant reading for the skilled scientist looking for guidance as to how a peptidyl boronic acid may be stabilised to form a pharmaceutically useful species. This can be explained by the fact that Wienand and Shoichet relate to early-stage creation of new active principles and not to formulating them.

35. The much more relevant teachings are those of Wu and Gupta. It will be recalled in this regard that Wu points away from combining boronic acid drugs with a base, because alkaline conditions are described as promoting instability, whereas Gupta points towards stabilizing boronic acid drugs as D-mannitol esters. The skilled person had no reason to expect that the presently described peptidyl boronic acid salts would provide enhanced stability of the parent acid.

36. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Respectfully submitted,

Anthony James Kennedy

Anthony James Kennedy, Ph.D.

Date 24th September 2007

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Millennium Pharmaceuticals, Inc.

VELCADE™ (bortezomib) for Injection

Prescribing Information

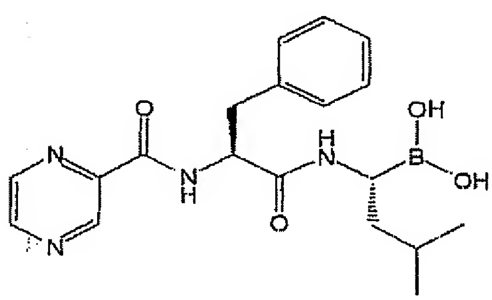
DESCRIPTION

VELCADE™ (bortezomib) for Injection is an antineoplastic agent available for intravenous injection (IV) use only. Each single dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl]boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is; $C_{19}H_{25}BN_4O_4$ The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8mg/mL in a pH range of 2-6.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted

proteolysis which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in non-clinical tumor models, including multiple myeloma.

Pharmacokinetics

Following intravenous administration of 1.3 mg/m^2 dose, the median estimated maximum plasma concentration of bortezomib was 509 ng/mL (range=109-1300 ng/mL) in eight patients with multiple myeloma and creatinine clearance values ranging from 31-169 mL/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to 15 hours at doses ranging from 1.45 to 2.00 mg/m^2 in patients with advanced malignancies. The pharmacokinetics of bortezomib as a single agent have not been fully characterized at the recommended dose in multiple myeloma patients.

Distribution

The distribution volume of bortezomib as a single agent was not assessed at the recommended dose in patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.

Metabolism

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination

The pathways of elimination of bortezomib have not been characterized in humans.

Special Populations

Age, Gender, and Race: The effects of age, gender, and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment: No pharmacokinetic studies were conducted with bortezomib in patients with hepatic impairment (see **PRECAUTIONS**).

Renal Impairment: No pharmacokinetic studies were conducted with bortezomib in patients with renal impairment. Clinical studies included patients with creatinine clearances values ranging from 13.8 to 220 mL/min (see **PRECAUTIONS**).

Pediatric: There are no pharmacokinetic data in pediatric patients.

Drug Interactions:

No formal drug interaction studies have been conducted with bortezomib.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 (see **PRECAUTIONS**).

Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of > 30 μM (> 11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC_{50}=18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme.

Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

CLINICAL STUDIES

Clinical Study in Relapsed and Refractory Multiple Myeloma

The safety and efficacy of VELCADE were evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. The median number of prior therapies was six. Baseline patient and disease characteristics are summarized in **Table 1.**

An IV bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8 treatment cycles. The study employed dose modifications for toxicity (see **DOSAGE AND ADMINISTRATION**). Patients who experienced a response to VELCADE treatment were allowed to continue VELCADE treatment in an extension study.

Table 1: Summary of Patient Population and Disease Characteristics *

	N=202
Patient Characteristics:	
Median Age in Years (Range)	59 (34,84)
Gender: Male/Female	60%/40%
Race: Caucasian/Black/Other	81%/10%/8%
Karnofsky Performance Status Score ≤ 70	20%
Hemoglobin <100 g/L	44%
Platelet count <75 x 10^9/L	21%
Disease Characteristics:	
Type of myeloma (%): IgG/IgA/Light chain	60%/24%/14%
Median β_2-microglobulin (mg/L)	3.5
Median Creatinine Clearance (mL/min)	73.9
Abnormal Cytogenetics	35%
Chromosome 13 Deletion	15%
Median Duration of Multiple Myeloma Since Diagnosis in Years	4.0
Previous Therapy	
Any Prior Steroids, e.g., dexamethasone, VAD	99%
Any Prior Alkylating Agents, e.g., MP, VBMCP	92%
Any Prior Anthracyclines, e.g., VAD, mitoxantrone	81%
Any Prior Thalidomide Therapy	83%
Received at Least 2 of the Above	98%
Received at Least 3 of the Above	92%
Received All 4 of the Above	66%
Any Prior Stem Cell Transplant /Other High-dose Therapy	64%
Prior Experimental or Other Types of Therapy	44%

*Based on number of patients with baseline data available

Responses to VELCADE alone are shown in **Table 2**. Response rates to VELCADE alone were determined by an independent review committee (IRC) based on criteria published by Blade and others[1]. Complete response required < 5% plasma cells in the marrow, 100% reduction in M protein, and a negative immunofixation test (IF-). Response rates using the SWOG criteria are also shown. SWOG response required a ≥ 75% reduction in serum myeloma protein and/or ≥ 90% urine protein[2]. A total of 188 patients were evaluated for response; 9 patients with nonmeasurable disease could not be evaluated for response by the IRC. Five patients were excluded from the efficacy analyses because they had minimal prior therapy.

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m^2. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study; while

33 % of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of VELCADE treatment beyond confirmation. The mean number of cycles administered was six.

The median time to response was 38 days (range 30 to 127 days).
The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

Table 2: Summary of Disease Outcomes

Response Analyses (VELCADE monotherapy) N=188	N (%)	(95% CI)
Overall Response Rate (Blade) (CR + PR)	52 (27.7%)	(21, 35)
Complete Response(CR)[1]	5 (2.7%)	(1, 6)
Partial Response(PR)[2]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	**365 Days**	**(224, NE)**

[1] **Complete response** required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

[2] **Partial Response** requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

[3] **Clinical Remission (SWOG)** required ≥75% reduction in serum myeloma protein and/or ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

In this study, the response rate to VELCADE was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities.

A small dose-response study was performed in 54 patients with multiple myeloma received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

INDICATIONS AND USAGE

VELCADE™ (bortezomib) for Injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

The effectiveness of VELCADE is based on response rates (**see CLINICAL STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.

WARNINGS

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Pregnancy Category D

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m^2 based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m^2) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory, although cases of mixed sensori-motor neuropathy have also been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening during treatment with VELCADE. Patients should be monitored for symptoms of

neuropathy, such as a burning sensation, hyperesthesia, hypesthesia, paresthesia, discomfort or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE (see **DOSAGE AND ADMINISTRATION**). Limited follow-up data regarding the outcome of peripheral neuropathy are available. Of the patients who experienced treatment emergent neuropathy more than 70% had previously been treated with neurotoxic agents and more than 80% of these patients had signs or symptoms of peripheral neuropathy at baseline (Also see **ADVERSE REACTIONS**).

Hypotension: VELCADE treatment can cause orthostatic/postural hypotension in about 12% of patients. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids.

Gastrointestinal Adverse Events: VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting **(see ADVERSE REACTIONS)** sometimes requiring use of antiemetics and antidiarrheals. Fluid and electrolyte replacement should be administered to prevent dehydration.

Thrombocytopenia: Thrombocytopenia, which occurred in about 40% of patients throughout therapy, was maximal at day 11 and usually recovered by the next cycle. Complete blood counts including platelet counts should be frequently monitored throughout treatment. Onset is most common in Cycles 1 and 2 but can continue throughout therapy. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE induced thrombocytopenia. VELCADE treatment may be temporarily discontinued if patients experience Grade 4 thrombocytopenia. VELCADE may be reinitiated at a reduced dose after resolution of thrombocytopenia (see **DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS**).

Patients with Hepatic Impairment:

Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with VELCADE.

(see CLINICALPHARMACOLOGY/Pharmacokinetics-Special Populations)

Patients with Renal Impairment:

No clinical information is available on the use of VELCADE in patients with creatinine clearance values less than 13 mL/min and patients on hemodialysis. These patients should be closely monitored for toxicities when treated with VELCADE (see **CLINICAL PHARMACOLOGY/Pharmacokinetics-Special Populations**).

Animal Toxicity Findings:

Cardiovascular toxicity

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12-14 hours post dose. Doses $\geq$ 1.2 mg/m^2 induced dose proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration

In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1 week rest) toxicities observed included severe anemia and thrombocytopenia, gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

Information for Patients

Physicians are advised to discuss the following with patients to whom VELCADE will be administered.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability: Since VELCADE may be associated with fatigue, dizziness, syncope, orthostatic/postural hypotension, diplopia or blurred vision, patients should be cautious when operating machinery, including automobiles.

Pregnancy/Nursing: Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breast feeding during treatment with VELCADE.

Dehydration/Hypotension: Since patients receiving VELCADE therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

Concomitant Medications: Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

Peripheral Neuropathy: Patients should be instructed to contact their physician if they experience new or worsening symptoms of peripheral neuropathy (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug Interactions

No formal drug interaction studies have been conducted with VELCADE.

In vitro studies with human liver microsomes indicate that bortezomib is a substrate for cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Patients who are concomitantly receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy (see **CLINICAL PHARMACOLOGY/Pharmacokinetics-Drug Interactions**).

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

There have been several SAE reports since filing. These reports were submitted to the IND. If the Agency feels this information is unnecessary, the language can be removed.

Drug Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at doses ≥ 0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2. VELCADE could have a potential effect on either male or female fertility.

Pregnancy Category D (see **WARNINGS**)

Nursing Mothers

It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VELCADE, women should be advised against breast feeding while being treated with VELCADE.

Pediatric Use:

The safety and effectiveness of VELCADE in children has not been established.

Geriatric Use:

Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%) of patients aged 65 years or older experienced responses versus 32% in patients under the age of 65. Across the 256 patients analyzed for safety, the incidence of Grade 3 or 4 events reported was 74%, 80%, and 85% for patients ≤ 50 years, 51 to 65 years, and > 65 years, respectively.

ADVERSE REACTIONS

The two studies described **(see Clinical Studies)** evaluated 228 patients with multiple myeloma receiving VELCADE 1.3 mg/m^2/dose twice weekly for 2 weeks followed by a 10-day rest period (21 day treatment cycle length) for a maximum of 8 treatment cycles.

The most commonly reported adverse events were asthenic conditions (including fatigue, malaise and weakness) (65%), nausea (64%), diarrhea (51%), appetite decreased (including anorexia) (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (37%), pyrexia (36%), vomiting (36%), and anemia (32%). Fourteen percent of patients experienced at least one episode of grade 4 toxicity, with the most common toxicity being thrombocytopenia (3%) and neutropenia (3%).

Serious Adverse Events (SAEs): Serious Adverse Events are defined as any event, regardless of causality that: results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability or is deemed to be an important medical event. A total of 113 (50%) of the 228 patients experienced SAEs during the studies. The most commonly reported SAEs included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

Adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 18% of patients. The reasons for discontinuation included peripheral neuropathy (5%), thrombocytopenia (4%), diarrhea (2%), and fatigue (2%).

Two deaths were reported and considered by the investigator to be possibly related to study drug: one case of cardiopulmonary arrest and one case of respiratory failure.

The most common adverse events are shown in **Table 3**. All adverse events occurring at ≥ 10% are included. In the single arm studies conducted it is often not possible to distinguish adverse events that are drug-caused and those that reflect the patient's underlying disease. See discussion of specific adverse reactions following **Table 3**.

Table 3: Most Commonly Reported (≥10% Overall) Adverse Events (N=228)

Adverse Event	All Patients (N = 228) [n (%)]		
	All Events	Grade 3 Events	Grade 4 Events
Asthenic conditions	149 (65)	42 (18)	1 (<1)
Nausea	145 (64)	13 (6)	0
Diarrhea	116 (51)	16 (7)	2 (<1)
Appetite decreased	99 (43)	6 (3)	0
Constipation	97 (43)	5 (2)	0
Thrombocytopenia	97 (43)	61 (27)	7 (3)
Peripheral neuropathy	84 (37)	31 (14)	0
Pyrexia	82 (36)	9 (4)	0
Vomiting	82 (36)	16 (7)	1 (<1)
Anemia	74 (32)	21 (9)	0
Headache	63 (28)	8 (4)	0
Insomnia	62 (27)	3 (1)	0
Arthralgia	60 (26)	11 (5)	0
Pain in limb	59 (26)	16 (7)	0
Edema	58 (25)	3 (1)	0
Neutropenia	55 (24)	30 (13)	6 (3)
Paresthesia and dysesthesia	53 (23)	6 (3)	0
Dyspnea	50 (22)	7 (3)	1 (<1)
Dizziness (excluding vertigo)	48 (21)	3 (1)	0
Rash	47 (21)	1 (<1)	0
Dehydration	42 (18)	15 (7)	0
Upper respiratory tract infection	41 (18)	0	0
Cough	39 (17)	1 (<1)	0
Bone pain	33 (14)	5 (2)	0
Anxiety	32 (14)	0	0
Myalgia	32 (14)	5 (2)	0
Back pain	31 (14)	9 (4)	0
Muscle cramps	31 (14)	1 (<1)	0
Dyspepsia	30 (13)	0	0
Abdominal pain	29 (13)	5 (2)	0
Dysgeusia	29 (13)	1 (<1)	0
Hypotension	27 (12)	8 (4)	0
Rigors	27 (12)	1 (<1)	0
Herpes zoster	26 (11)	2 (<1)	0
Pruritus	26 (11)	0	0
Vision blurred	25 (11)	1 (<1)	0
Pneumonia	23 (10)	12 (5)	0

Asthenic conditions (fatigue, malaise, weakness)

Asthenia was reported in 65% of patients and was predominantly reported as Grade 1 or 2. The first onset of fatigue was most often reported during the 1st and 2nd cycles of therapy. Asthenia was Grade 3 for 18% of patients. Two percent of patients discontinued treatment due to fatigue.

Gastrointestinal Events

The majority of patients experienced gastrointestinal adverse events during the studies, including nausea, diarrhea, constipation, and vomiting. Grade 3 or 4 gastrointestinal events occurred in 21% of patients and were considered serious in 13% of patients. Vomiting and diarrhea each were of Grade 3 severity in 7% of patients and were Grade 4 in <1%. Five percent of patients discontinued due to gastrointestinal events. Appetite decreased (anorexia) was reported as an adverse event for 43% of patients. The incidence of Grade 3 decreased appetite was 3%.

Thrombocytopenia

Thrombocytopenia was reported during treatment with VELCADE for 43% of patients. The thrombocytopenia was characterized by a dose related decrease in platelet count during the VELCADE dosing period (Days 1 to 11) with a return to baseline in platelet count during the rest period (Days 12 to 21) in each treatment cycle. Thrombocytopenia was Grade 3 or 4 in intensity for 27% and 3% respectively of patients. Four percent (4%) of patients discontinued VELCADE treatment due to thrombocytopenia of any grade.

Peripheral Sensory Neuropathy

Events reported as peripheral neuropathy, peripheral sensory neuropathy, and peripheral neuropathy aggravated occurred in 37% of patients. Peripheral neuropathy was Grade 3 for 14% of patients with no Grade 4 events. New onset or worsening of existing neuropathy was noted throughout the cycles of treatment. Six percent (6%) of patients discontinued VELCADE due to neuropathy. More than 80% of all study patients had signs or symptoms of peripheral neuropathy at baseline evaluation. The incidence of Grade 3 neuropathy was 5% (2 of 41 patients) in patients without baseline neuropathy. Symptoms may improve or return to baseline in some patients upon discontinuation of VELCADE. The complete time-course of this toxicity has not been fully characterized.

Pyrexia

Pyrexia (> 38°C) was reported as an adverse event for 36% of patients and was assessed as Grade 3 in 4% of patients.

Neutropenia

Neutropenia occurred in 24% of patients and was grade 3 in 13% and grade 4 in 3%. The incidence of febrile neutropenia was <1%.

Hypotension

Hypotension (including reports of orthostatic hypotension) was reported in 12% of patients. Most events were Grade 1 or 2 in severity. Grade 3 hypotension occurred in 4% of patients; no patient experienced Grade 4 hypotension. Patients developing orthostatic hypotension did not have evidence of orthostatic hypotension at study entry; half had pre-existing hypertension and one third had evidence of peripheral neuropathy. Doses of antihypertensive medications may need to be adjusted in patients receiving VELCADE. Four percent of patients experienced hypotension, including orthostatic hypotension, and had a concurrent syncopal event.

Serious Adverse Events from Clinical Studies

In approximately 580 patients, the following serious adverse events (not described above) were reported, considered at least possibly related to study medication, in at least one patient treated with VELCADE administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.

Blood and lymphatic system disorders: Disseminated intravascular coagulation

Cardiac disorders: Atrial fibrillation aggravated, atrial flutter, cardiac amyloidosis, cardiac arrest, cardiac failure congestive, myocardial ischemia, myocardial infarction, pericardial effusion, pulmonary edema, ventricular tachycardia

Gastrointestinal disorders: Ascites, dysphagia, fecal impaction, gastritis hemorrhagic, gastrointestinal hemorrhage, hematemesis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute

Hepatobiliary: Hyperbilirubinemia, portal vein thrombosis

Immune system disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity

Infections and Infestations: Bacteremia

Injury, poisoning and procedural complications: skeletal fracture, subdural hematoma

Metabolism and nutrition disorders: Hypocalcemia, hyperuricemia, hypokalemia, hyponatremia, tumor lysis syndrome

Nervous system: Ataxia, coma, dizziness, dysarthria, dysautonomia, cranial palsy, grand mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression, transient ischemic attack

Psychiatric: Agitation, confusion, psychotic disorder, suicidal ideation

Renal and urinary: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria urinary incontinence, urinary retention, renal failure, acute and chronic, glomerular nephritis proliferative

Respiratory, thoracic and mediastinal: Acute respiratory distress syndrome, atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, respiratory failure

Vascular: Cerebrovascular accident, deep venous thrombosis, peripheral embolism, pulmonary embolism

OVERDOSAGE

Cardiovascular safety pharmacology studies in monkeys show that lethal IV doses are associated with decreases in blood pressure, increases in heart rate, increases in contractility, and ultimately terminal hypotension. In monkeys, doses of 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in progressive hypotension starting at 1 hour and progressing to death by 12 to 14 hours following drug administration.

No cases of overdosage with VELCADE were reported during clinical trials. Single doses of up to 2.0 mg/m^2 per week have been administered in adults. In the event of overdosage, patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure and body temperature (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

There is no known specific antidote for VELCADE overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of VELCADE is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21) (see **CLINICAL STUDIES section for a description of dose administration during the trials**).

This 3-week period is considered a treatment cycle. At least 72 hours should elapse between consecutive doses of VELCADE.

Dose Modification and Reinitiation of Therapy:

VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below (see **PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1.0 mg/m^2/dose; 1.0 mg/m^2/dose reduced to 0.7 mg/m^2/dose). The following table contains the recommended dose modification for the management of patients who experience VELCADE-related neuropathic pain and/or peripheral sensory neuropathy **(Table 4)**. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk/ benefit assessment.

Table 4: Recommended Dose Modification for VELCADE-related neuropathic pain and/or peripheral sensory neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1.0 mg /m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue VELCADE

NCI Common Toxicity Criteria website – http://ctep.info.nih.gov/reporting/ctc.html

Administration Precautions: VELCADE is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage.

Reconstitution/Preparation for Intravenous Administration: Prior to use, the contents of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection, USP. The reconstituted product should be a clear and colorless solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Stability: Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light.

VELCADE contains no antimicrobial preservative. When reconstituted as directed, VELCADE may be stored at 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Reconstituted VELCADE should be administered within eight hours of preparation. The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to three hours in a syringe, however total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

HOW SUPPLIED

VELCADE (*bortezomib*) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of *bortezomib* as a white to off-white cake or powder.

NDC 63020-049-01	3.5 mg single dose vial

STORAGE

Unopened vials may be stored at controlled room temperature 25° C (77° F); excursions permitted from 15 to 30° C (59 to 86° F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Caution: Rx only.

U.S. Patents: 5,780,454, 6,083,903, 6,297,217

Distributed and Marketed by: Millennium Pharmaceuticals, Inc.
75 Sidney St.
Cambridge, MA 02139

MILLENNIUM™

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VELCADE™ (bortezomib) for Injection

Patient Information

VELCADE is intended for use under the guidance and supervision of a health care professional. Please discuss the possibility of the following side effects with your doctor:

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability: VELCADE may be associated with fatigue, dizziness, light-headedness, fainting or blurred vision. Please exercise caution or avoid operating machinery, including automobiles, following use of VELCADE.

Pregnancy/Nursing: Please use effective contraceptive measures to prevent pregnancy and avoid breast feeding during treatment with VELCADE.

Deydration/Hypotension: Following the use of VELCADE therapy, you may experience vomiting and/or diarrhea. Drink plenty of fluids. Speak with your doctor if these symptoms occur and what you should do to control or manage these symptoms.

If you experience symptoms of dizziness or light-headedness, consult a healthcare professional. Seek immediate medical attention if you experience fainting spells.

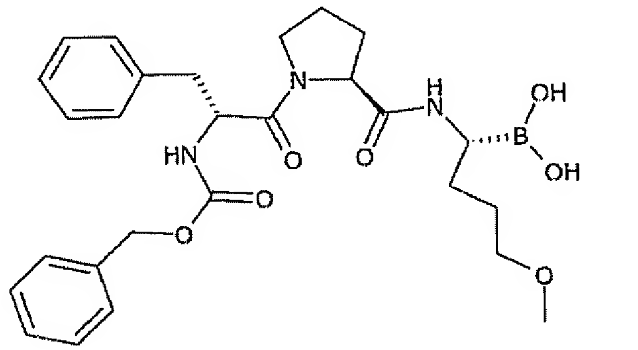
Concomitant Medications: Please speak with your doctor about any other medication you are currently taking. Your doctor will want to be aware of any other medications.

Peripheral Neuropathy: Contact your doctor if you experience new or worsening symptoms of peripheral neuropathy, such as numbness, pain, or a burning feeling in the feet or hands.

APPENDIX A

SUMMARY STABILITY REPORT FOR TRI 50c

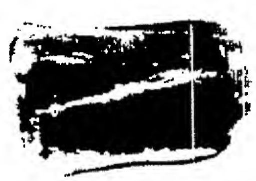
TRI 50c is a boronic acid of the following structure:



(R,S,R)-TRI 50c Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)$_2$

Table 1 : Appearance

Stability Condition	Time point		
	Initial	1 month	3 month
-20°C	White	White	White
25°C/60%RH		White	Brown
30°C/70%RH		Yellow/Brown	Dark Brown
40°C/75%RH		Brown	Dark Brown



Tri50c-00-Stab01
Storage condition 30°C/70%RH

Tri50c-00-Stab01
Storage condition 40°C/75%RH

Figure 1 Appearance of TRI50c-00 at 30°C/70% r.h. and 40°C/75% r.h. after 1 month

Table 2 : Degradation Profile

Temperature		-20°C	-20°C	25°C	25°C	30°C	30°C	40°C	40°C
Time [month]	0	1	3	1	3	1	3	1	3
% content in sample (HPLC)	97.18	96.74	99.11	83.17	58.83	67.79	44.39	62 53	43.15

SUMMARY STABILITY REPORT FOR TRI 50c SODIUM SALT

	T = 0	T = 1 -20°C	T = 1 25°C/75% r.h.	T = 1 40°C/75% r.h.	T = 3 -20°C	T = 3 25°C/60% r.h.	T = 3 40°C/75% r.h.
Color	White	White	White	White	White	White	Brown
% content in sample	101.5	102.6	98.9	88.4	102.5	95.3	48.6

Curriculum Vitae

Dr Tony Kennedy

Family Information

Age 59. Married with 3 children .
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Professional Career

Vice President Development Trigen Ltd – since April 2002.

Past Work Experience

Roche 1997-2002

- Global Head of Project Management, Roche Pharma.
- Member of the Pharma Strategic Marketing Management Team
- Member of the Roche Development Committee

The Global Project Management group comprised 30 staff located in Basel, Nutley USA and Welwyn UK. The group provides project management for Roche's international development teams (LifeCycle Teams). As Head of Project Management I managed the LifeCycle Teams Goal setting and performance assessment process. As a member of the Development Committee and the Pharma Strategic Marketing Management Team I

participated actively in the review and valuation of the Roche Portfolio and in prioritisation and allocation of resources.

Earlier Responsibilities at Roche

- Site Head Project Management Group Roche Welwyn UK
- Global Project Leader for Tamiflu (Neuraminidase inhibitor for influenza)

Headhunted to Roche in April 1997 to lead the Tamiflu development team. The project was a top development priority for Roche being in direct competition with Glaxo's flu drug Relenza but substantially behind in development. I led this team from phase 1 trials to NDA filing (April1999). The Team took the drug from first entry in man to NDA filing in 2 years. The first marketing approval was granted in September 1999 and US NDA approval was in October 1999 3.5 years after the discovery of the molecule. Entering the US market the same flu season as Glaxo's Relenza it established market dominance in the first year.

SmithKline Beecham (1988 – 1997)

Project Director and Head of Project Management Cluster

Responsibility for leading Worldwide Project Teams in several therapeutic areas including anti-infectives (Augmentin, novel carbapenem antibiotics, metallo betalactamase inhibitors) cardiovasculars (Eminase and novel thrombolytics), lipid modifying agents (ACAT inhibitors, sequestrants), gastrointestinal projects (reversible/irreversible proton pump inhibitors including Pantoprazole), anti-diabetic agents (Avandia) and immunomodulators for cancer indications. These projects included biologicals and small molecule NCE's, spanned all development phases including life cycle management and included co-development projects with US, European and Japanese Pharma companies.

Non Project Responsibilities

Project Management representative on SB 'Breakthrough Teams' redesigning development processes to fast track projects and meet market needs.

Established and led the highly acclaimed SB 'Drug Development Simulation Training Programme' which trained over 700 staff in the USA and UK from all areas of Pharma about commercially focused product development.

Roche Products Ltd Welwyn (1977-1987)

Development Project Leader 1984-87

Project leader for Project Teams which included a novel immunomodulator anti-rheumatic agent and the ACE inhibitor Cilazapril. Local team leader for Roferon-A.

Senior Research Pharmacologist 1977-1984

Research work in autoimmune inflammation. Establishment of in vitro and in vivo immune assays for T and B cell function and selection of development leads. Discovery Project Team leader from 1980 for 3 projects. My experimental work contributed to the progression into development of 3 drugs and to patents.

Academic Background

M.R.C. Post Doctoral Research Fellow, The School of Pharmacy, London University
PhD. Biochemistry London University
MSc. Neurochemistry London University
BSc. Biochemistry Surrey University

My research work is described in over 30 publications.

Pharmaceutical Project Management Interests

- Proposed and Edited 'Pharmaceutical Project Management' (Marcel Dekker 1998). 2nd Edition to be released 2008.
  - the first book devoted to this topic!
- Founder Member of the steering group of the UK Pharmaceutical Industry Project Management Group.

- Chairman of the 'Effective Project Management' Seminars run quarterly by Management Forum in London in the decade from 1989.

Personal Interests
Travel, antiques, keeping fit (old English meaning).